REMARKS

Entry of this Amendment and reconsideration of the subject application in view thereof are respectfully requested.

I. Interview with Examiner Wollenberger

Applicant thanks Examiner Wollenberger for the courtesies extended during the telephone interview on June 12, 2007 with Applicant's attorneys, Nanda P.B.A. Kumar and Stanley P. Fisher, and inventor Igor E. Bondarev. The prior art of record, claim rejection under 35 U.S.C. § 103 and proposed amendments were discussed during the interview.

II. Claim Status

Claims 1-58 were pending in the application. Of these, claims 3, 5, 18, 20, 30-35 and 41-58 were withdrawn, claims 1, 2, 4, 6-17, 19, 21-29, and 36-40 were rejected and claims 2, 17, 24, 26-28 and 37 were objected to. Claims 1, 2, 6, 7, 10, 16, 17, 21, 22, 24, 25-27, 29 and 37 have been amended to clarify the invention. Claims 4, 19, 28, 39 and 40 have been canceled without prejudice or disclaimer. No new matter is added.

III. Response to Final Office Action of June 13, 2006

Applicant respectfully believes that the claim objections and rejections made in the Final Office Action of June 13, 2006 (Part of Paper No./Mail Date 20060525) (herein referred to as "the Office Action" or "this Office Action" or "the present Office Action") have been either overcome or rendered moot in view of the following discussion:

1. Claim Objections

Claims 2, 17, 24, 26-28, and 37 were objected to again because the claims recite limitations to non-elected inventions such as an antisense sequence or an antisense compound, a construct capable of expressing human L1RT antisense sequence, an inorganic compound, and peptide. Claims 2, 6, 17 and 21 were objected to under 37 C.F.R. § 1.75(c) as being of improper dependent form and claim 4 was objected to as being dependent on a withdrawn claim, claim 3.

Applicant respectfully believes that the entry of this amendment should overcome these

objections. Withdrawal of these objections is respectfully requested.

2. Rejections Under 35 USC § 112, Second Paragraph

Claims 16 and 28 stood rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 16 was rejected for reciting the limitation of "the organic compound" and the rejection of claim 28 was maintained for reciting the limitation of "a protein comprising SEQ ID NO: 1."

Applicant respectfully believes that entry of the presently amended claims should overcome the rejections under 35 U.S.C. § 112, second paragraph of these claims. Accordingly, reconsideration and removal of the rejections are respectfully requested.

3. Rejections Under 35 USC § 112, First Paragraph, Written Description

Claims 1, 2, 4, 6, 8, 9, 16, 17, 19, 21, 23 and 25 stood rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement for reasons stated on pages 4-6 of the Office Action.

The Examiner noted on page 6 of the Office Action that "[r]emoving the recitation 'nucleoside analog' from claims 1 and 16 and amending claims 2, 6, 17 and 21 to properly limit the invention of claims 1 and 16, respectively, would overcome this rejection." Applicant respectfully believes that the entry of the revised claims presented herein should overcome this rejection.. submits that the recitation 'nucleoside analog' has been deleted from claims 1 and 16, and claims 2, 6, 17 and 21 have been amended to limit the invention of claims 1 and 16.

The Examiner maintained the rejection of claims 1, 2, 4, 6-15, 39 and 40 as failing to comply with the written description requirement. In particular, the Examiner contends that "Applicants have not described a representative number of cancers that are 'due to' or 'induced by' LINE-1 RT or set forth any guidance as to how to identify all such cancers."

In response, Applicant respectfully submits again that the patent specification is written for a person of skilled in the art, and such a person is deemed to come to the patent with the knowledge of what has come before. *In re GPAC Inc.*, 57 F.3d 1573, 1579 (Fed. Cir. 1995).

Applicant points out that it is not necessary to spell out every detail of the invention including every cancer treatable by the claimed methods in the specification to satisfy section 112, first paragraph. The written description requirement is that only enough must be included to convince a person of skill in the art that the inventor possessed the invention. Therefore, Applicant respectfully submits that, after reading the patent application as filed, a person of skill in the art would understand how to make and use the methods and would understand the Applicant to have invented the methods set forth in claims 1, 2, 4, 6-15, 39 and 40. There is no violation of the written description requirement.

Notwithstanding, without conceding the validity of the rejection and solely to expedite the prosecution of the present patent application, Applicant has elected to revise claim language, which revisions are believed to address the Examiner's concerns regarding the written description requirement.

Accordingly, reconsideration and withdrawal of the written description rejections are respectfully requested.

4. Rejections Under 35 USC § 112; First Paragraph, Enablement

Claims 39 and 40 are rejected under 35 U.S.C. § 112, first paragraph, as failing to satisfy enablement requirement. In view of the Applicant's election to cancel these claims, this rejection is moot.

5. Rejections Under 35 U.S.C. § 103

Claims 1, 2, 4, 6-17, 19, 21-29, and 36-38 stood rejected under 35 U.S.C. 103(a) as being unpatentable over Wagner et al., 1997, *Cancer Res.* 57:2341-2345 ("Wagner"), Delap et al., 1991, P*roc. Annu. Meet. Am. Soc. Clin. Oncol.* 10:A295, Doroshow et al., 1994, *Proc. Annu. Meet. Am. Soc. Clin. Oncol.* 13:146, Gomez et al., 1998, *Biochemical Biophysical Res. Comm.* 246:107-110, Bryan et al., 1997, *Nature Medicine* 3:1271-1274 ("Bryan 1997a"), Bryan et al., 1997, *Eur. J. Cancer* 33:767-773 ("Bryan 1997b") and Kuo et al., 1998, *Biochemical Biophysical Res. Comm.* 253:566-570. Applicant respectfully traverses this rejection for at least the following reasons:

A. The prior art relied upon does not disclose, suggest, or render obvious the claimed invention, either individually or when combined

The Examiner asserts that the prior art is replete with reports teaching, demonstrating, and suggesting the use of AZT, either alone or in conjunction with other agents, to treat cancers of different types. The Examiner cites the Wagner Delap and Doroshow references.

Wagner teaches that AZT inhibits MNU induced rat mammary carcinomas *in vivo*. Wagner states that "AZT alone may have therapeutic potential as an anti-breast cancer chemotherapeutic agent." However, Wagner does not teach or suggest a method claimed in each of claims 1, 10, 16, 24, and 37. In particular, for example, Wagner does not teach or suggest a method of treating cancer showing alternative lengthening of telomeres in cancer cells or telomerase negative cancer cells using an inhibitor or antagonist (e.g., a nucleoside analog or AZT) of L1RT (the terms "inhibitor(s) or antagonist(s)" are defined terms). The inhibitor or antagonist is one that blocks the lengthening of telomeres in telomerase negative cancer cells.

Delap discloses a phase I study of AZT in 11 patients with cancer (4 breast, 3 colorectal, 1 ENT, 2 lung, 1 sarcoma). Of these, 3 patients have noted improvement in their cancer-related symptoms. Doroshow discloses a phase I study of AZT and cisplatin in 25 patients with cancer. Tumor types included GI (8 patients), lung (5 patients), breast (3 patients), ovary (2 patients), and other (7 patients). Of these, 7 patients responded with a stable disease. However, neither Delap nor Doroshow teaches or suggests a method claimed in each of claims 1, 10, 16, 24, and 37. In particular, neither Delap nor Doroshow teaches or suggests a method wherein AZT is used to block the lengthening of telomeres in telomerase negative cancer cells. Neither Delap nor Doroshow remedies the deficiency of Wagner.

The Examiner also contends that the "prior art teaches or the least suggests that both telomerase positive and telomerase negative cells are present in a number of cancers," and cites two references; Bryan 1997a and Bryan 1997b.

Bryan 1997a reports evidence for an alternative mechanism for maintaining telomere length (alternative lengthening of telomeres) in human tumors and tumor-derived cell lines. It discloses that out of 57 human tumor specimens assayed, telomerase was detected in 69% of the tumors and the remaining being telomerase negative (see Table 1, page 1271) and that ALT occurs in at least a small proportion of human tumors. It discloses that 2 out of 56 renal

carcinomas were telomerase negative and 5 out of 47 melanomas lacked telomerase activity. It also discloses that "ALT exists when telomerase is absent" (see page 1271, left column). Thus, Bryan 1197a teaches or suggests that the majority of tumors are telomerase positive tumors and the proportion of human tumors with ALT is small. Bryan 1997b is a review and reports the current understanding of the involvement of telomerase in *in vitro* immortalized human cells. It discloses that approximately a quarter of *in vitro* immortalized cell lines so far examined have no detectable telomerase activity. With regard to tumor-derived cell lines, it discloses that "all 110 tumor-derived cell lines [assayed] had telomerase activity" and a further 54 cell lines derived from a variety of tumors that were assayed revealed three cell lines that lacked telomerase activity. It states that "ALT functions as an alternative to telomerase in human tumour development, albeit in a very small minority of tumours."

Applicant's invention concerns tumors with ALT. However, neither Bryan 1997a nor Bryan 1997b teaches or suggests a method claimed in each of claims 1, 10, 16, 24, and 37. In particular, neither Bryan 1997a nor Bryan 1997b teaches or suggests a method wherein AZT blocks the lengthening of telomeres in telomerase negative cancer cells. Neither Bryan 1997a nor Bryan 1997b remedies the deficiency of Wagner.

Gomez is cited as teaching that AZT causes telomere shortening in cells culture and that "AZT must be viewed as a telomerase inhibitor with potential anticancer properties." However, Gomez does not teach or suggest a method claimed in each of claims 1, 10, 16, 24, and 37. In particular, Gomez does not teach or suggest a method wherein AZT blocks the lengthening of telomeres in telomerase negative cancer cells. Gomez does not remedy the deficiency of Wagner.

Kuo is cited as teaching that "L1 transcripts are present in a large number of solid tumors and tumor cell lines. However, Kuo does not teach or suggest a method claimed in each of claims 1, 10, 16, 24, and 37. In particular, Kuo does not teach or suggest a method wherein AZT is used to block the lengthening of telomeres in telomerase negative cancer cells. Kuo does not remedy the deficiency of Wagner.

Thus, the prior art relied upon does not disclose, suggest, or render obvious the claimed invention, either individually or when combined.

B. The inherency argument fails because obviousness cannot be predicated on what is unknown

The Examiner appears to admit that none of the cited references teaches that the reverse transcriptase encoded by L-1 (LINE-1) retrotransposon is involved in lengthening of telomeres in cancer cells. The Examiner also appears to admit that none of the cited references teaches that AZT blocks lengthening of telomeres in such cells. However, the Examiner contends on page 19 of the Office Action that, for prima facie showing, it is inconsequential that AZT inhibits telomerase as well as L1- encoded reverse transcriptase "since such properties are inherent to AZT and necessarily flow from the disclosed methods for treating breast cancer." This statement is an unsupported conclusion.

The Examiner points to no extrinsic evidence that makes clear that the missing descriptive matter - L1RT is involved in the lengthening of telomeres in cancer cells and AZT is an inhibitor of this enzyme, and that AZT can block the lengthening of telomeres in telomerase negative cells – is necessarily present in the Wagner, Delap and Dorshow references and that it would be so recognized by persons of ordinary skill in the art. Inherency may not be established by probabilities or possibilities.

The combined teachings of Bryan et al., (the extrinsic evidence) show that ALT occurs in a small proportion of human tumors and ALT functions as an alternative to telomerase in human tumour development, albeit in a very small minority of tumours. For example, Bryan 1997a, *Nat. Med.* 3, 1271-1274) reports ALT activity occurred in 29% of the human breast tumor specimens assayed. Thus, the extrinsic evidence indicates that there is a 29% chance (not 100%) that a given human breast tumor shows ALT activity. While the cancers described by the Wagner, Delap and Dorshow references may be ALT, such properties do not necessarily flow from the disclosed methods for treating breast cancer and are not "inherent" in Wagner, Delap or Dorshow. The Examiner must consider both the invention and the prior art references as a whole. MPEP § 2141.02. "The mere fact that a certain thing may result from a given set of circumstances is not sufficient" to establish inherency. *In re Oelrich,* 666 F.2d 578, (CCPA 1981). "That which may be inherent is not necessarily known." *In re Spormann,* 363 F.2d 444 (CCPA 1966); MPEP § 2141.02.

C. AZT was not known as an inhibitor of L1RT activity and to block the lengthening of telomeres in telomerase negative cells at the time of the present invention

It was known in the art at the time of the present invention that telomerase activity is present in most cancers and telomerase as a diagnostic target and to administer AZT to inhibit telomerase activity (see, for example, U.S. Patent 5707795; U.S. Patent 6004939, Melana et al., 1998, Clinical Cancer Research, 4:693-696; Herbert et al., 2001, Breast Cancer Research, 3:146-149; Gellert et al., 2005, Drug Discovery Today: Disease Mechanisms, 2(2):159-164, a copy each of which is included as part of the Information Disclosure Statement filed with the Patent Office on June 13, 2007). It was also known in the art that not all studies with AZT targeted to telomerase activity demonstrated progressive telomere shortening. See Gellert et al., 2005. It was further known in the art that AZT has no effect on the telomere length in telomerase negative cells (Saos-2 cells) (*see* Gan et al., 2002, FEBS Lett. 527:10-14). What was not known at the time of the present invention, however, is that L1RT is involved in the lengthening of telomeres in cancer cells and AZT is an inhibitor of this enzyme, and that AZT can block the lengthening of telomeres in telomerase negative cells. Obviousness cannot be predicated on what is unknown." *Id.*; See also MPEP § 2141.02.

D. Applicant proceeded against the art accepted wisdom, and achieved telomere shortening in telomerase negative cells and their growth inhibition

The use of AZT to treat ALT cancers was not an identified and predictable solution. Stated otherwise, there is no suggestion to use AZT to treat an individual suffering from cancer showing alternative lengthening of telomeres in cancer cells, and in so using there is no reasonable expectation of success. This is because, at the time of the present invention, AZT has been reported to have no effect on the telomere length in telomerase-negative cells (*see* Gan et al., 2002, FEBS Lett. 527:10-14).[1] This prior art disclosure discredits or otherwise discourages the solution claimed. Therefore, this option was not within the technical grasp of a person of

[1] See also the previous Office Action dated, October 12, 2005 (Part of Paper No./Mail Date 20050922), page 16, where the Examiner acknowledged that "[i]t is noted that the teachings of Gan et al. appear to contradict the teachings of the instant application. Namely, Gan et al. teach that AZT has no effect on telomere length in Saos-2 cells, whereas Applicants teach that AZT does affect telomere length in Saos-2 cells."

ordinary skill in the art and that person has no good reason to pursue this option. Nevertheless, Applicant proceeded against this art accepted wisdom, and achieved telomere shortening in telomerase negative cells and their growth inhibition. Proceeding contrary to accepted wisdom in the art is itself evidence of nonobviousness. *Arkie Lures, Inc. v. Gene Larew Tackle, Inc.*, 119 F.3d 953 (Fed.Cir. 1997).

E. A *prima facie* case of obviousness has not been established and the claimed invention is nonobvious

In view of the above discussion, the Examiner has not established that the combined teachings of the cited references would have suggested to one of ordinary skilled in the art that L1RT is involved in the lengthening of telomeres in cancer cells and AZT is an inhibitor of this enzyme, and that AZT can block the lengthening of telomeres in telomerase negative cells. Applicant respectfully points out again that it is the invention as a whole, and not some part of it, which must be obvious under 35 U.S.C. § 103.

Accordingly, Applicant respectfully submits that the Examiner has not established a *prima facie* case of obviousness of independent claims 1 10, 16, 24, and 37 under 35 U.S.C. § 103(a). Even if prima facie obviousness has been established, which it has not, it is urged that the combination of the cited references fails to render the present invention obvious under a proper § 103 analysis, as one skilled in the art cannot arrive at the claimed invention by combining the cited references.

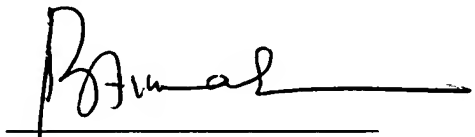
Further, the rejected dependent claims 2, 6-9, 11-17, 21-23, 25-27, 29, 36 and 38 are similarly considered by Applicant to patentably define themselves over the cited references by virtue of their dependency from the respective independent claims and also because these dependent claims add additional limitations. As such, claims 2, 6-9, 11-17, 21-23, 25-27, 29, 36 and 38 stand in condition for allowance for these very same reasons. Reconsideration and withdrawal of this rejection are respectfully requested.

IV. Conclusion

Applicant believes this response to be a full and complete response to the Office Action. Accordingly, favorable reconsideration in view of this response and allowance of all of the pending claims are earnestly solicited.

If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,



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